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## Notes

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## Second Cancers Among Long-term Survivors of Non-Hodgkin's Lymphoma

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**Background:** Patients with non-Hodgkin's lymphoma (NHL) are at increased risk for second cancers. Few studies, however, include long-term survivors, and none report risk for second cancer among NHL patients surviving 15 or more years.

**Purpose:** Our aim was to examine the pattern of second cancers among long-term survivors of NHL.

**Methods:** A cohort of 6171 patients diagnosed with NHL as a first primary cancer and who survived 2 or more years was identified within population-based tumor registries in Sweden, Ontario, and Iowa and within the affiliated tumor registry of The Netherlands Cancer Institute. Nearly 1000 NHL patients lived 15 or more years after diagnosis. Tumor registry files were searched for new invasive primary malignancies. **Results:** Second cancers were reported in 541 subjects (observed-to-expected ratio [O/E] = 1.37; 95% confidence interval = 1.26-1.49), with significant excesses seen for all solid tumors (O/E = 1.28), acute nonlymphocytic leukemia (O/E = 4.83), melanoma (O/E = 2.38), Hodgkin's disease (O/E = 12.0), and cancers of the lung (O/E = 1.36), brain (O/E = 2.33), kidney (O/E = 2.07), and bladder (O/E = 1.77). Among 15-year survivors, significantly increased risks persisted for all second cancers (O/E = 1.45), solid tumors (O/E = 1.37), bladder

cancer (O/E = 3.24), and Hodgkin's disease (O/E = 25.0). The actuarial risk of developing a second cancer 3-20 years after diagnosis of NHL was 21%, compared with a population expected cumulative risk of 15%. **Conclusions:** Patients with NHL continue to be at significantly elevated risk of second primary cancer for up to two decades following diagnosis. The pattern of risk suggests the influence of treatment as well as factors associated with the underlying disease. **Implications:** Quantitative studies of second cancer following NHL are needed to clarify the role of antecedent therapy, shared risk factors, host susceptibility, and other etiologic and diagnostic influences. Despite the generally advanced age of patients with NHL, the persistently elevated risk of second cancers should alert clinicians to the importance of continued medical surveillance. [*J Natl Cancer Inst* 85:1932-1937, 1993]

Surveys (1,2) of patients with non-Hodgkin's lymphoma (NHL) have reported increased risks of second malignant neoplasms. For solid tumors, the temporal pattern of excesses in the largest study to date appeared related to the radiotherapy and/or chemotherapy administered for NHL, with upswings in risk in 10-year survivors (2). Studies of the pattern of cancer excesses among long-term survivors, however, have been limited, and no investigation reports risks among NHL patients surviving for 15 or more years (1-9). To evaluate further the risk of second cancers among long-term survivors of NHL, we identified a cohort of 6171 2-year survivors from several countries.

## Patients and Methods

NHL patients who were diagnosed from January 1, 1965, through December 31, 1980, were identified from three population-based cancer registries (the State Health Registry of Iowa, The Ontario Cancer Registry, and The

\*See "Notes" section following "References."

Swedish Cancer Register) and from the affiliated tumor registry of The Netherlands Cancer Institute; 1980 was chosen as the last eligible year of NHL diagnosis to allow sufficient follow-up (through 1989) for the development of subsequent solid tumors. Persons included in the study were (a) between 18 and 70 years of age at the time of NHL diagnosis, (b) had no invasive cancer prior to NHL, (c) resided in the catchment area of the cancer registry, and (d) survived 2 or more years following diagnosis without the development of a second invasive primary malignancy. In order to facilitate retrieval of NHL treatment data for future case-control studies, it was also required that patients had received initial management at specified major hospitals.<sup>1</sup> Designated institutions in Ontario included the Princess Margaret Hospital<sup>2</sup> and the eight Regional Cancer Centers.<sup>2</sup> In Iowa,<sup>3</sup> the institutions that treated the largest numbers of NHL patients included two hospitals in Des Moines (Iowa Methodist Medical Center [1973-1980] and Mercy Hospital [1973-1980]), The University of Iowa Hospitals and Clinics (1965-1980) in Iowa City, and Mercy Medical Center (1973-1980) in Cedar Rapids. In The Netherlands, study patients were treated at the affiliated hospital of The Netherlands Cancer Institute in Amsterdam.

Cancer registry incidence files were searched to identify invasive second malignancies<sup>4</sup> following NHL (10-13). Subsequent diagnoses of lymphocytic leukemia were not evaluated, since they could represent progression of the initial malignancy. Chronic granulocytic leukemias and myeloid leukemias not specified as acute or chronic were included in the category "other nonlymphocytic leukemia." These diagnoses were grouped with leukemias in which the cell type was not specified and with acute nonlymphocytic leukemias to form the category "all leukemia."

Person-years of observation were compiled according to age, sex, and calendar year periods from 2 years after the date of NHL diagnosis to the date of death, date of diagnosis of a second cancer, or the end of study (December 31, 1989), whichever occurred first. Incidence rates generated by each registry were multiplied by the accumulated person-years at risk for patients from that registry to estimate the number of cancer cases expected. The observed and expected numbers of second cancers from all registries were then combined.

Statistical tests and 95% confidence intervals (CIs) were based on the assumption that cases followed a Poisson distribution. Tests for homogeneity and linear trend were conducted according to the methods described by Breslow et al. (14). Cumulative probabilities of developing second malignancies over time were calculated utilizing life table methods (15). To determine the absolute risk of second cancers, we subtracted the expected number of second cancers from the number observed; we then divided the difference by the person-years of follow-up and multiplied the quotient by 10<sup>4</sup> to yield the excess number of cancers expected per 10000 persons per year. Second cancer risks, both overall and by site, were evaluated by age, sex, registry, and calendar year.

## Results

A cohort of 6171 two-year survivors of NHL was identified, with approximately 49% and 34% of patients provided by Sweden and Ontario, respectively. There were 3449 men and 2722 women. The average age at diagnosis for all NHL patients was 56.1 years, and the mean follow-up time was 7.4 years. Second primary cancers occurred in 541 patients, compared with 394.9 expected (observed-to-expected ratio of second cancers [O/E] = 1.37) (Table 1). Risk did not vary by registry. Five hundred two (92.8%) second cancers were microscopically confirmed. The average duration between diagnoses of NHL and secondary cancer was 8.4 years (median, 7.5 years).

Significantly elevated risks were observed for all leukemia, acute nonlymphocytic leukemia, Hodgkin's disease, melanoma, and cancers of the lung, kidney, bladder, and brain and other central nervous system. No cancer occurred significantly below expectation.

The risk of all second malignant neoplasms was greater in men (O/E = 1.51) than in women (O/E = 1.18). Excesses of rectal cancer were limited to men. Whereas increased risks for lung cancer were present in both sexes, only those in men were statistically significant. Women exhibited elevated risks for connective tissue neoplasms, albeit based on small numbers. Cancers of the breast and female genital tract occurred slightly below expectation.

Risks of second cancers grouped by time since diagnosis of NHL are shown in Table 2. The O/E ratios for all subsequent cancers were significantly elevated in each follow-up interval, ranging from 1.32 to 1.45 (*P* trend = .60). Similarly, significant increases in the risk of solid tumors were apparent in the 2- to 4-year period and did not diminish with time, even among 15-year survivors (*P* trend = .44). In contrast to the uniform relative risk across latency intervals, the absolute excess of solid tumors (per 10000 persons per year) increased with time since diagnosis of NHL, from 15 during the 2- to 4-year interval to 24, 30, and 40, respectively, during the

three subsequent follow-up periods.

The cumulative risk of any second primary cancer by time since NHL diagnosis is shown in Fig. 1. The actuarial risks of developing a solid tumor or any second primary cancer were 19.3% and 21.1%, respectively, 3-20 years following NHL diagnosis. The corresponding population expected cumulative risks were 15.0% and 15.4%, respectively.

Among long-term (15-year) survivors, elevated risks of second cancers were restricted to men (observed [O] = 38; O/E = 1.79; 95% CI = 1.27-2.46), with persistent excess malignancies of the bladder and all digestive tract sites taken together. The O/E ratio for second cancers among women surviving 15 or more years was 1.0 (95% CI = 0.57-1.63). The relative risk of all second cancers among 15-year survivors was not significantly different among various age groups; those who were the youngest (ages 18-39 years) at diagnosis of NHL, in whom only six second malignancies occurred, were not more likely to develop subsequent cancers than were older patients.

Elevated risks for bladder cancer became apparent during the 5- to 9-year follow-up interval, reaching threefold among 15-year survivors (*P* trend = .02). Significant excesses of bladder cancer persisted among 20-year survivors (O = 3; O/E = 8.33). Acute nonlymphocytic leukemia was reported in 14 NHL patients, with significantly increased risks observed in the intervals of 2-4 years and 5-9 years. Although excesses continued in 10-year survivors, only two cases of acute nonlymphocytic leukemia were observed. Elevated risks for lung cancer peaked in the 5- to 9-year interval and declined to a level below expectation after 15 years of follow-up.

Increased risks were present throughout most latent periods for other cancers exhibiting significant overall excesses (i.e., melanoma, Hodgkin's disease, and cancers of the kidney and brain and other central nervous system). Of the 22 subsequent cases of Hodgkin's disease, 21 were microscopically confirmed. Twenty-three renal cell cancers were evident, but no tumors originated in the renal pelvis or ureter. Eighteen of the 21 brain and

Table 1. Observed numbers and relative risks of second cancers\* among patients with NHL†

Cancer type or site	Men‡		Women‡		Total‡		95% CI
	O	O/E	O	O/E	O	O/E	
All second cancers	344	1.51§	197	1.18§	541	1.37§	1.26-1.49
All solid tumors	307	1.40§	179	1.11	486	1.28§	1.18-1.41
All buccal	12	1.36	6	2.17	18	1.56	0.92-2.46
Esophagus	5	1.47	2	1.98	7	1.58	0.63-3.26
Stomach	18	1.41	6	1.02	24	1.29	0.82-1.91
Colon	29	1.38	21	1.13	50	1.26	0.93-1.66
Rectum	22	1.75§	7	0.92	29	1.44	0.96-2.06
Liver, gallbladder	6	1.24	2	0.42	8	0.84	0.36-1.65
Pancreas	8	1.00	4	0.71	12	0.88	0.45-1.54
Larynx	4	0.95	1	2.17	5	1.08	0.35-2.51
Lung	64	1.41§	13	1.13	77	1.36§	1.07-1.69
Sex-specific sites							
Female breast	—	—	41	0.89	41	0.89	0.64-1.21
All female genital	—	—	26	0.91	26	0.91	0.60-1.34
Uterine cervix	—	—	4	0.82	4	0.82	0.22-2.09
Uterine corpus	—	—	12	0.96	12	0.96	0.50-1.68
Ovary	—	—	8	0.85	8	0.85	0.37-1.68
Prostate	47	0.99	—	—	47	0.99	0.73-1.32
Testis	1	1.27	—	—	1	1.27	0.02-7.04
Kidney	15	2.08§	8	2.06	23	2.07§	1.31-3.11
Bladder	30	1.72§	9	1.97	39	1.77§	1.26-2.42
Melanoma	13	2.74§	7	1.91	20	2.38§	1.45-3.67
Brain and central nervous system	10	2.00	11	2.72§	21	2.33§	1.44-3.56
Thyroid	1	1.04	2	1.14	3	1.11	0.22-3.25
Bone	0	0	1	3.85	1	1.47	0.02-8.18
Connective tissue	1	0.70	4	4.08§	5	2.08	0.67-4.86
Hodgkin's disease	16	13.68§	6	8.96§	22	12.02§	7.53-18.20
Multiple myeloma	4	1.15	4	1.58	8	1.33	0.57-2.63
All leukemia	17	4.53§	8	3.19§	25	3.99§	2.58-5.90
Acute nonlymphocytic leukemia	10	5.88§	4	3.33	14	4.83§	2.64-8.10
Other nonlymphocytic leukemia	2	1.98	3	4.84	5	3.03	0.98-7.07
All other cancers¶	21	1.73	8	0.91	29	1.39	0.93-1.99

\*Excludes diagnoses of NHL or lymphocytic leukemia.

†International Classification of Diseases for Oncology morphology codes 9590-9642, 9670-9710, and 9750.

‡O = observed numbers of second cancers; O/E = observed-to-expected ratio of second cancers; CI = confidence interval.

§P&lt;.05.

||Excludes diagnoses of Hodgkin's disease, multiple myeloma, and all leukemia.

¶Includes 29 cancers of unknown or ill-defined primary site.

Table 2. Second cancers\* grouped by time following initial NHL diagnosis

Years after NHL diagnosis .....	2-4		5-9		10-14		≥15	
No. of patients starting interval .....	6171		4496		2635		977	
Person-years within interval .....	15739		18144		8609		3302	
Cancer type or site	O	O/E	O	O/E	O	O/E	O	O/E
All second cancers	150	1.32†	218	1.39†	119	1.37†	54	1.45†
All solid tumors‡	133	1.21†	194	1.28†	110	1.31†	49	1.37†
All buccal	7	1.96	7	1.53	2	0.83	2	2.00
Stomach	8	1.39	7	0.96	8	2.04	1	0.58
Colon	13	1.21	20	1.27	11	1.19	6	1.50
Rectum	5	0.85	11	1.37	8	1.80	5	2.63
Pancreas	2	0.51	7	1.31	3	0.99	0	—
Lung	23	1.38	36	1.57†	15	1.22	3	0.61
Female breast§	15	1.11	16	0.87	7	0.70	3	0.73
All female genital§	8	0.87	10	0.89	5	0.88	3	1.33
Uterine corpus§	6	1.51	3	0.60	2	0.79	1	1.02
Prostate§	10	0.85	15	0.80	15	1.31	7	1.33
Kidney	7	2.13	8	1.81	5	2.09	3	2.94
Bladder	4	0.65	18	2.05†	10	2.02	7	3.24†
Melanoma	5	2.15	10	2.98†	4	2.12	1	1.20
Brain and central nervous system	7	2.48†	9	2.52†	3	1.62	2	2.53
Hodgkin's disease	8	12.50†	10	13.89†	1	3.03	3	25.00†
All leukemia	6	3.31†	13	5.24†	5	3.60†	1	1.69
Acute nonlymphocytic leukemia	4	5.00†	8	6.90†	2	3.08	0	—

\*Excludes diagnoses of NHL or lymphocytic leukemia. Only those sites at which 10 or more cancers were observed are listed. O = observed; O/E = observed-to-expected ratio of second cancers.

†P&lt;.05.

‡Excludes diagnoses of Hodgkin's disease, multiple myeloma, and all leukemia.

§Calculations are based on sex-specific person-years of follow-up and sex-specific incidence rates.

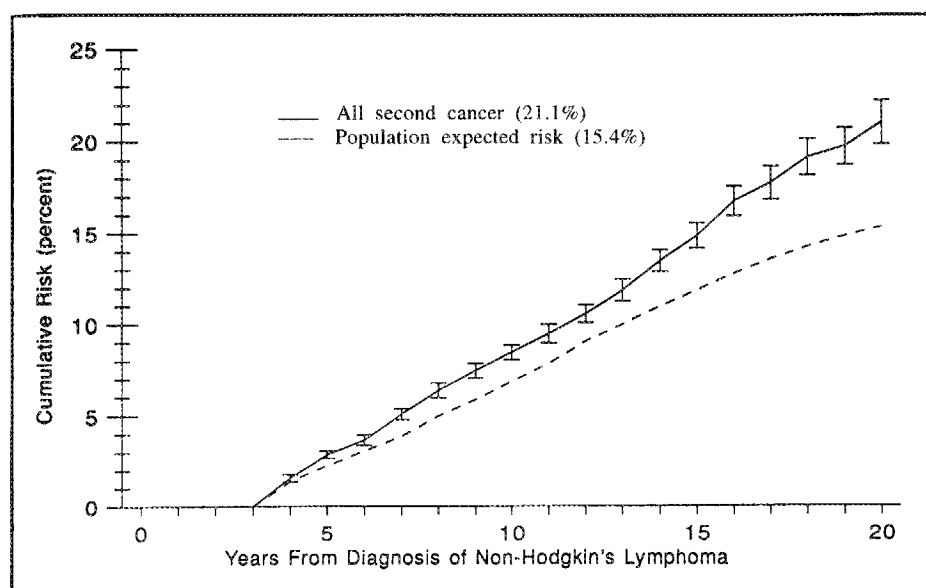


Fig. 1. Cumulative risk of all second primary cancers among 6171 two-year survivors of NHL. (Second cancers occurring less than 2 years after NHL diagnosis are not included in the estimates.) The percentages in parentheses indicate the actuarial risk at 20 years.

other central nervous system tumors were histologically confirmed.

## Discussion

This is the first study of second malignant neoplasms among patients with NHL that includes large numbers of 15-year survivors (1-9). A new observation is the elevated risk of second cancers among NHL patients followed up to 20 years, with no evidence of a diminution of risk over time. Approximately one in five 2-year survivors would be expected to develop a new cancer between 2 and 20 years following initial diagnosis of NHL, indicating the need for follow-up throughout life.

In contrast to the relatively flat pattern of risk over time seen in our series, an upswing in second cancer risk was observed among 10-year survivors of NHL reported to the Surveillance, Epidemiology, and End Results (SEER) Program<sup>5</sup> of the National Cancer Institute (NCI) (1973-1987) (2). However, extended follow-up of these patients indicates that the risk of subsequent malignancies in the 10- to 15-year interval ( $O/E = 1.49$ ) is now similar to that observed in the 5- to 9-year period ( $O/E = 1.32$ ) (Travis LB, Curtis RE, Hankey BF, et al.: unpublished data). Few NHL patients within the SEER Program cohort have yet survived 15 years.

The overall magnitude of the risk for second cancers in our study was similar to that noted among NHL patients reported to the Connecticut Tumor Registry (1935-1982) ( $O/E = 1.3$ ) (1) and the SEER Program (1973-1987) ( $O/E = 1.2$ ) (2). In contrast, other investigations (3-5,7-9) have not found excess risks of all second cancers following NHL; however, several of these studies antedated the use of treatment regimens that improved survival (3,4), while others either lacked statistical power (5,8) or had incomplete follow-up of patients (9).

In general, elevated risks of second cancer may reflect not only the late sequelae of treatment, but also the effects of host susceptibility, shared etiologic factors, increased clinical surveillance, or other factors (16). The possible contributions of these and other influences on the elevated risk of second cancer following NHL are discussed below by site.

Several studies have linked bladder cancer (2,17,18) and acute non-lymphocytic leukemia (6,19,20) to NHL therapy. Our report is one of the first, however, to demonstrate that bladder cancer risk remains significantly elevated among 15- and 20-year survivors of NHL, possibly reflecting the high cumulative doses of alkylating agents such as cyclophosphamide which may be given to NHL patients (17).

Although significant excesses of acute nonlymphocytic leukemia and preleukemia have been reported among patients with NHL (2,6-9,19,20), most estimates have been based on fewer than 10 cases (6-9,19,20). Our  $O/E$  ratio of 4.83 for secondary acute nonlymphocytic leukemia, derived from a larger number of patients ( $n = 14$ ), likely represents a minimal estimate of risk, since there has been a tendency among cancer registries to under-report the occurrence of acute nonlymphocytic leukemia following NHL (21). Moreover, several of the acute leukemias in our study in which the cell type was not specified ( $n = 6$ ) may have represented acute nonlymphocytic leukemia but were not included in risk calculations. Excesses of acute non-lymphocytic leukemia in our study persisted among 10-year survivors, as found in other series (2,6,7), but were not evident among patients surviving 15 or more years. This wave-like pattern of risk is similar to that seen for radiogenic leukemia and suggests that treatment with alkylating agents and/or radiotherapy may have been responsible for these excesses of acute nonlymphocytic leukemia.

The early excess risks of lung cancer in our study and other surveys of NHL (1,2) are not consistent with the usual latency of radiogenic solid tumors, which begin to rise in incidence 10 years following exposure (22). A similar temporal pattern is also evident for the occurrence of lung cancer following Hodgkin's disease (10,23), and lymphoma patients with second lung cancers are usually smokers (6,10,23-26). Some have suggested that chemotherapy for Hodgkin's disease might possibly be linked to the early appearance of subsequent lung cancers (27) and other solid tumors (28), although similar findings have not been reported among NHL patients. The association between subsequent lung cancer and NHL may partly reflect shared etiologic factors. One survey (29) reported a significant relationship between number of cigarettes smoked and mortality from NHL, although other investigations (30-32) linking tobacco use with NHL have not reported dose-response gradients. Still other studies (33-35) have found no

association between tobacco use and NHL. Further investigations of second lung cancers are needed to clarify the role of various influences and to explore the possible interaction of smoking, radiotherapy, and immunosuppression (23).

Excesses of renal cancer in our survey were observed during all follow-up intervals after NHL, similar to results in the SEER Program (2). Case reports (36-39) have suggested that cyclophosphamide may induce tumors of the renal pelvis or ureter, but all 23 tumors in our series arose from renal parenchyma. Although the mechanisms responsible for the increased occurrence of renal cell cancer are unknown, further studies should evaluate not only causal factors (e.g., chemotherapeutic agents), but also the possible role of diagnostic surveillance during management of NHL.

Increased risks of malignant melanoma were previously reported in patients with Hodgkin's disease (23,40) and chronic lymphocytic leukemia (41) as well as in those with NHL (1,2,9). The risk of melanoma is probably influenced by immunologic defects associated with various lymphoproliferative malignancies (42-45). It is noteworthy that both NHL (46,47) and melanoma (48) occur excessively in association with therapeutic immunosuppression, as seen with renal transplantation. Some melanomas arising in immunocompromised patients have been shown to evolve from dysplastic nevi (40,48).

A significant excess of brain and other central nervous system cancer following NHL was previously noted only in data from the Connecticut Tumor Registry (1). Whether the increase that we observed in histologically confirmed brain and other central nervous system tumors following NHL might be due to radiotherapy (22) or other factors is not clear.

The elevated risk of Hodgkin's disease following NHL in our study confirms observations within the SEER Program (2,49), although misclassification may contribute to the excess noted here, given the complexities of lymphoma diagnosis. Elevated risks of NHL following Hodgkin's disease have also been reported (50), as has the occurrence of composite NHL and

Hodgkin's disease (51). The interrelationship between NHL and Hodgkin's disease was recently reviewed by Jaffe et al. (52).

In summary, results from this international survey indicate that patients with NHL are at increased risk of second primary cancers. The risk of subsequent malignancies remains high in 15-year survivors, who demonstrate a 45% excess of all cancer. Extended follow-up should further characterize the temporal distribution of site-specific risks. Quantitative studies of second cancers following NHL are needed to clarify the role of antecedent therapy, shared risk factors, host susceptibility, and other etiologic and diagnostic influences. In the interim, the persistently elevated risk of second cancers for up to two decades following NHL diagnosis should alert clinicians to the importance of continued medical surveillance.

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## Notes

<sup>1</sup>Because of the unique nature of the health care delivery system in Sweden, which facilitates retrieval of treatment data, all NHL patients in Sweden who met study entry criteria were included.

<sup>2</sup>Patients from the study by Lishner et al. (9) who met entry criteria for this investigation are included in the current report. The Regional Cancer Centers are located in Hamilton, Kingston, London, Ottawa, Sudbury, Thunder Bay, Toronto, and Windsor.

<sup>3</sup>A portion of the patients registered with the Iowa Surveillance, Epidemiology, and End Results Program were included in a previous report (2).

<sup>4</sup>Since benign tumors of the brain and other central nervous system are included in Swedish cancer incidence rates, all such neoplasms following the occurrence of NHL in Swedish patients are also included in our analyses.

<sup>5</sup>*Ed. note:* SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the NCI. Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

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## Synergism and Lack of Cross-resistance Between Short-term and Continuous Exposure to Fluorouracil in Human Colon Adenocarcinoma Cells

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**Background:** Our recent findings in vitro in the human colon adenocarcinoma cell line HCT-8 suggest that resistance to fluorouracil (5-FU) in patients with advanced colorectal cancer might be overcome by use of a different treatment schedule. **Purpose:** We tested the hypothesis that HCT-8 cells resistant to short-term 5-FU exposure retain sensitivity to continuous exposure and studied interactions between the two schedules. **Methods:** HCT-8 cell lines resistant to short-term (pulse) treatment with 5-FU or to continuous exposure were obtained by six exposures to different concentrations of 5-FU for 4 hours or 7 days. We used a monolayer clonogenic assay to determine 5-FU-induced cell kill in resistant HCT-8 cells and sensitive parent cells. Parent cells were exposed to different concentrations of 5-FU for 1, 4, or 24 hours (short term), for 7 days (continuous exposure), or in a combination of both types of schedules. In a

\*See "Notes" section following "References."